Noxious Heat and Scratching Decrease Histamine-Induced Itch and Skin Blood Flow

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The aim of this study was to assess the effect of thermal stimuli or distal scratching on skin blood flow and histamine-induced itch in healthy volunteers. Twenty-one healthy volunteers participated in the study. Baseline measurements of skin blood flow were obtained on the flexor aspect of the forearm. These measurements were compared with skin blood flow after various stimuli: heating the skin, cooling the skin, noxious cold 2°C, noxious heat 49°C, and scratching via a brush with controlled pressure. Afterwards histamine iontophoresis was performed and skin blood flow and itch intensity were measured immediately after the above-mentioned stimuli. Scratching reduced mean histamine-induced skin blood flow and itch intensity. Noxious heat pain increased basal skin blood flow but reduced histamine-induced maximal skin blood flow and itch intensity. Cold pain and cooling reduced itch intensity, but neither affected histamine-induced skin blood flow. Sub-noxious warming the skin did not affect the skin blood flow or itch intensity. These findings suggest that heat pain and scratching may inhibit itch through a neurogenic mechanism that also affects skin blood flow.

Key words: itch/scratching/pain/skin blood flow
J Invest Dermatol 125:1268–1272, 2005

Patients who suffer from chronic itch often report diverse and creative means to alleviate it, including hot and very cold showers (Bernhard, 1994; Yosipovitch, 2003). The inhibition of itch by noxious thermal stimuli, as well as mechanical means such as scratching, has been demonstrated in experiments in animal models and humans (Murray and Waver, 1975; Fruhstorfer *et al*, 1986; Ward *et al*, 1996; Jinks and Carstens, 1997; Mochizuki *et al*, 2003; Yosipovitch *et al*, 2003). In addition, warming the skin can exacerbate itch, whereas cooling the skin ordinarily suppresses it (Jinks and Carstens, 1997; Mizumura and Koda, 1999). Both thermal stimuli and scratching modulate itch by inhibiting either primary afferents or second-order neurons (Ward *et al*, 1996; Carstens, 1997; Jinks and Carstens, 1997). Histamine application induces itch by activation of histamine-sensitive C fibers afferents (Schmelz *et al*, 1997); in addition, it induces a strong vasodilatatory effect through the flare response, which is part of the triple response of Lewis (1927). This response can be blocked by denervation and anesthesia (Baluk, 1997). It is well known that skin blood flow is significantly increased during mechanical scratching, warming, and noxious heat. Conversely, cooling reduces skin blood flow. Interestingly, no studies have yet examined the effect of these stimuli on blood flow during histamine iontophoresis and its correlation with itch perception. In this study, we present the unexpected finding that noxious heat pain and scratching—which increase basal skin blood flow—have an inhibitory effect on histamine-induced hyperemia at the same time that they reduce itch intensity. These stimuli were introduced to the skin distal to the site of histamine-induced hyperemia, suggesting that they may inhibit histamine-induced blood flow as well as itch through a neurogenic mechanism.

Results

Baseline skin blood flow measurements Table I summarizes the baseline perfusion measurements of skin with and without the external stimuli of warming, cooling, noxious heat, noxious cold, and scratching. The mean and peak perfusion (V) were significantly higher by 1.1 and 1.6 V, respectively, with noxious heat pain ($p < 0.001$). The maximum perfusion was higher by 0.5 V with scratching, but this did not reach a level of statistical significance. Warmth, cold, and cold pain stimuli did not significantly attenuate skin blood flow.

Skin blood flow measurements after histamine iontophoresis Table II summarizes the results of skin perfusion after histamine iontophoresis and the effect of external stimuli. Noxious heat pain reduced mean histamine-induced skin perfusion in 14 of the 21 subjects, as well as reducing mean peak perfusion by 1 V ($p = 0.02$). Distal scratching reduced perfusion in 12 of the 21 subjects. Scratching had a similar effect in reducing mean histamine-induced skin perfusion by 0.85 V ($p = 0.01$).

Representative scans of the effect of scratching and heat pain on histamine-induced skin blood flow in one subject are shown in Fig 1.

Noxious cold pain, cooling, as well as heating, did not significantly affect the mean or peak skin blood flow.

Table I. Blood flow measurements: mean and peak perfusion on the forearm with and without external stimuli of heat pain, cold pain, warming, cooling, and scratching

Perfusion units (V)	Basal blood flow	Sub-noxious warmth induction	Sub-noxious cold induction	Heat pain	Cold pain	Scratching
Mean	1.6 ± 0.7	1.5 ± 0.7	1.5 ± 0.9	2.7 ± 0.9	1.6 ± 0.9	1.9 ± 1.1
Difference from basal	—	−0.1 ± 0.8	−0 ± 0.9	−1.1 ± 0.9	−0. ± 1.1	0.2 ± 0.9
p-value	—	0.4	0.7	**<0.001**	0.9	0.1
Max	2.4 ± 0.9	2.4 ± 0.8	2.6 ± 1.4	4.0 ± 1.2	2.5 ± 1.5	2.9 ± 1.6
Difference from basal	—	0.0 ± 0.9	0.2 ± 1.4	1.6 ± 1.3	0.1 ± 1.6	0.5 ± 1.6
p-value	—	0.9	0.4	**<0.001**	0.6	0.1

Values are mean ± SD.

Validating skin blood flow measurements in repeat histamine iontophresis with and without heat pain stimuli and scratching We repeated heat pain stimuli as well as scratching in a group of five subjects who did not undergo these tests previously. This was done in order to rule out a possibility that an order effect or non-specific changes associated with a long period of test could affect the results. This test was done in a full randomized fashion. The results show that mean skin blood flow is significantly reduced with repetitive scratching from 2.2 ± 1.7 baseline to 1.0 ± 0.2; heat pain also significantly reduced skin blood flow to a mean of 1.2 ± 0.39. Maximal skin blood flow showed that histamine mean blood flow was reduced by scratching and heat pain from 3.8 ± 3.0 to 2.5 ± 1.4, and 2.4 ± 0.5, respectively, from which we surmise that heat pain and scratching have a significant inhibitory effect on histamine-induced skin blood flow.

Psychophysical measurements Not all the subjects experienced significant itch with histamine induction. No subjects reported itch from the baseline sham saline stimuli. Overall, 12 of the 21 subjects experienced itch more than 1 cm (10 cm VAS, measured at the end of each 5 min session).

Itch intensity was reduced by heat pain stimuli by 0.9 cm ($p = 0.003$), as well as cold pain stimuli (0.8 cm, $p = 0.009$), sub-noxious cold stimuli 0.6 cm ($p = 0.04$), and scratching (0.7 cm, $p = 0.04$) in the computerized visual analogue scale (COVAS) assessment. Non-noxious heat stimuli did not significantly affect itch intensity levels in psychophysical measurements. Table III summarizes the results of psychophysical measurements of itch intensity with and without the administration of the external stimuli. Based on subject reporting, itch subsided in all study participants within 10 min.

Correlation between itch intensity and skin blood flow Although itch intensity was lower after all stimuli except warmth, no correlation was noted overall between reduction of histamine blood flow and itch intensity.

Discussion

Noxious heat pain and scratching administered outside the site of histamine induction can reduce histamine-induced skin perfusion. This may suggest a neurogenic inhibition mediated by thermal nociceptors, which are mechanically sensitive.

Seventy years ago, Thomas Lewis (1927) described the triple response to histamine injection: wheal, edema, and flare. Since that time we have also learned that histamine, in addition to its strong vasodilatory effect, stimulates polymodal nociceptors (Torebjork, 1974) and activates itch-specific C nerve fibers (Schmelz *et al*, 1997). The ability of noxious stimuli to inhibit itch was originally recognized by Bickford (1937), who observed inhibition of itch resulting from noxious stimuli.

Table II. Blood flow measurements post-histamine iontophoresis: mean and peak perfusion on the forearm with and without external stimuli of warming, cooling, heat pain, cold pain, and scratching

Perfusion units (V)	Histamine blood flow	Histamine + warmth induction	Histamine + cold induction	Histamine + heat pain	Histamine + cold pain	Histamine + scratching
Mean	2.9 ± 1.3	2.4 ± 1.03	2.5 ± 0.8	2.3 ± 1.1	2.4 ± 0.8	2.1 ± 0.7
Difference from basal	—	−0.5 ± 1.5	−0.5 ± 1.2	−0.6 ± 1.4	−0.5 ± 1.4	−0.8 ± 1.5
p-value	—	0.12	0.07	0.05	0.1	**0.01**
Max	4.4 ± 1.7	3.6 ± 1.3	3.7 ± 1.3	3.4 ± 1.0	3.6 ± 1.1	3.3 ± 1.2
Difference from basal	—	−0.7 ± 1.8	−0.7 ± 1.3	−1.0 ± 1.8	−0.7 ± 1.61	−1.0 ± 1.6
p-value	—	0.09	0.1	**0.02**	0.08	**0.02**

Values are mean ± SD.

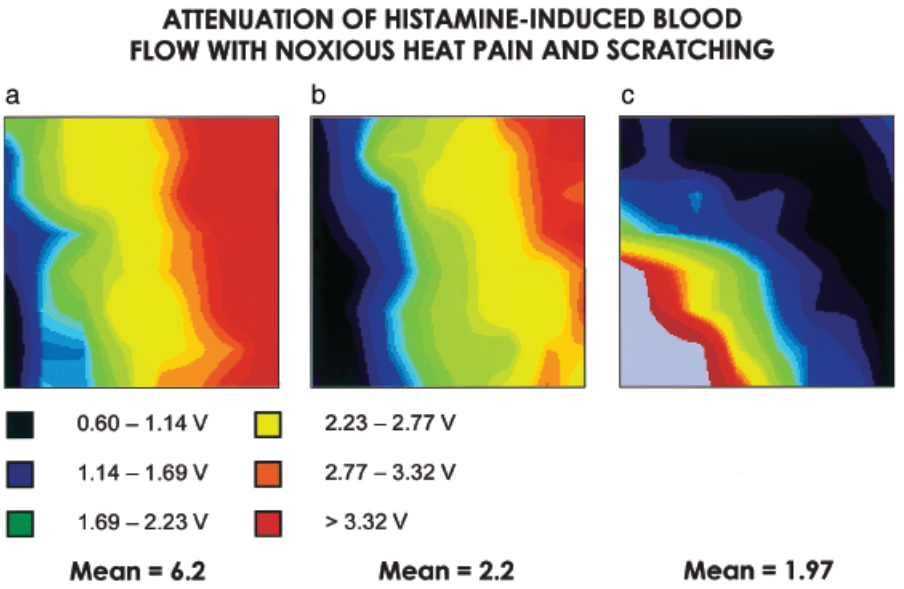


Figure 1
LDI maps of skin blood perfusion in the skin of the flexor forearm of a subject. (*a*) During baseline histamine iontophoresis: mean skin perfusion 6.2 ± 0.9. (*b*) During histamine heat pain stimuli: mean skin perfusion 2.5 ± 0.8. (*c*) During repetitive scratching: mean skin blood flow 1.9 ± 0.3. Histamine skin blood flow was reduced by heat pain as well as scratching (black and blue levels indicate low perfusion and yellow and red indicate high perfusion).

Noxious and innocuous counter stimuli—including mechanical stimuli which activate C nerve fibers—are capable of modulating the magnitude of itch response perceived by human subjects (Fruhstorfer *et al*, 1986; Ward *et al*, 1996). Patients often report that they use noxious heat, cold, and scratching to alleviate their itch (Yosipovitch, 2003). It could be argued that the interventions and measuring techniques of these psychophysiological techniques employed on skin attenuate the intensity of itch simply by causing distraction. Distraction could be an important factor influencing itch perception, especially when two different sensations are applied concurrently (Ward *et al*, 1996). The results of this study, however, provide firm support that these counter stimuli do not operate merely by masking the subjective sensation of itch. These counter stimuli were capable of inhibiting hyperemic skin blood flow—an objective measure.

The mechanism of such a response could be a peripheral inhibition of C nerve fibers, but because the response can be effected when the modulating stimulus is applied distal to the histamine application site, a centrally mediated suppressive mechanism could be considered (Murray and Weaver, 1975; Fruhstorfer *et al*, 1986; Ward *et al*, 1996; Jinks and Carstens, 1997). The striking effect of heat pain stimuli—which significantly increase the baseline skin blood flow but significantly decrease blood flow when histamine is present—further suggests that a neurogenic mechanism is in play.

Evidence for sensory nerve involvement in skin blood flow has been noted in post-occlusive reactive hyperemia in humans (Larkin and Williams, 1993). This reactive hyperemia was significantly decreased by pre-treatment with local anesthesia; however, local anesthesia did not block the local increase in skin blood flow induced by intradermally administered neuropeptides CGRP or topical capsaicin.

Other neurogenic mechanisms unrelated to an effect on skin perfusion can inhibit itch. These may include activating A delta fibers by cold pain and C mechanosensitive fibers. It has been previously suggested by Greaves and Wall (1996) that scratching or other sensory stimuli such as electrical stimuli can inhibit itch. Several studies have demonstrated that noxious stimuli remote from the painful area inhibit pain in humans and animals; these same mechanisms could presumably act in analogous fashion to inhibit itch. This phenomenon is often referred to as diffuse noxious inhibitory control (DNIC) (Le Bars, 1979a,b, 2002). DNIC involves the inhibition of multireceptive neurons in the dorsal horn of the spinal cord that results when a noxious stimulus is applied to a region of the body remote from the neuron's excitatory receptive field. These data suggest that DNIC are triggered specifically by activation of peripheral receptors whose signals are carried by A delta and C nerve fibers. This inhibition of pain can be elicited in any part of the body. A recent study has shown that a simultaneous itching and cold pain stimuli far away from an itchy area had a significant effect in reducing that itch. These interventions also

Table III. Itch intensity as measured by a computerized visual analogue scale during (VAS) histamine iontophoresis with and without external stimuli of warming cooling, noxious heat pain and cold pain, and scratching

VAS (10 cm)	Histamine baseline	Histamine + sub-noxious warmth induction	Histamine + sub-noxious cold induction	Histamine + heat pain	Histamine + cold pain	Histamine + scratching
Mean ± SD	1.4 ± 1.2	1.2 ± 1.2	0.9 ± 0.9	0.5 ± 0.6	0.6 ± 0.7	0.7 ± 0.7
Difference from baseline	—	−0.2 ± 0.8	−0.5 ± 1.1	−0.9 ± 1.2	−0.8 ± 1.2	−0.72 ± 1.0
p-value	—	NS	0.041	0.003	0.007	0.004

increased blood flow in the midbrain region, particularly the periaqueductal gray matter (PAG), an area that is usually not activated with itch alone, suggesting a central mechanism for noxious cold pain in inhibiting itch (Mochizuki *et al*, 2003).

Taken together our results suggest that histamine-induced skin blood flow and histamine-induced itch can be reduced when nerve fibers outside of an itchy area are activated by noxious heat stimuli or scratching. Certain other non-noxious stimuli did not have the same effect. These stimuli—particularly sub-noxious ones—may have different effects when applied directly, rather than distal to an itchy spot. This remains to be clarified. Moreover, development of new drugs that can alter skin hyperemic responses may be useful as antipruritic agents. The exact mechanism is as yet unclear.

Methods

Subjects Twenty-one healthy subjects (13 women and eight men) participated in the initial study. Five other subjects (four women and one man) participated in a short validation test. The study was conducted according to the Declaration of Helsinki Principles. All procedures were approved by the Institutional Review Board at Wake Forest University School of Medicine.

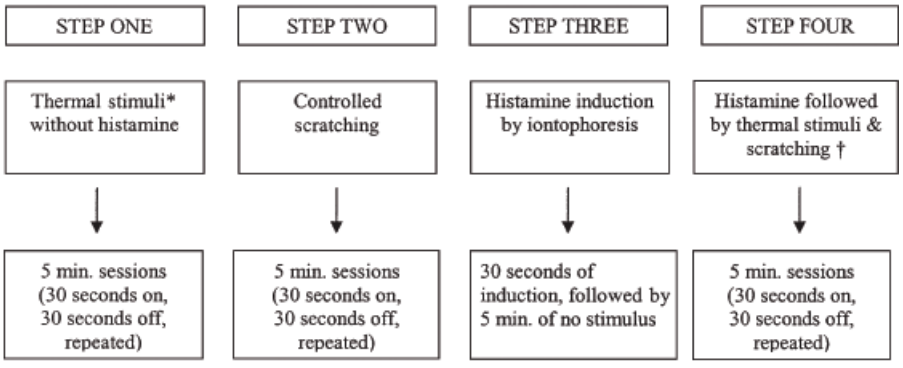
All volunteers provided written informed consent and were free to withdraw from the study at any time.

Histamine Histamine iontophoresis was achieved with a 1% solution dissolved in 2% methylcellulose gel (Sigma, St Louis, Missouri) delivered via a chamber incorporating a fine platinum wire (anode) connected to a constant current stimulator. A current of 200 μA for 30 s was used with the Perimed PF3826 Perilont Power device (Perimed, Stockholm, Sweden). A "sham" stimulus of 0.9% saline in 2% methylcellulose gel was first inotophoresed (also 200 μA for 30 s) into one of the sketched boxes to provide a baseline assessment of itch intensity.

Thermal and itch stimuli Thermal stimuli were delivered by a 16 × 16 mm Peltier device (Medoc, Ramat Yishai, Israel, TSA, 2001). Itch stimulation was performed with histamine iontophoresis.

Perfusion imaging with laser doppler imager Skin blood flow perfusion was mapped with a PIM II laser doppler perfusion imager (LDPI), which uses a low-power He–Ne laser beam with a wavelength of 632.5 nm. The mean and peak perfusion were calculated in an 8 × 8 mm area in the iontophoresis site.

a



* Thermal stimuli included: 2°C, 15°C, 41°C, 49°C
† 5 min. stimuli sessions began 30 sec. after completion of histamine induction.
Note: Measurements were conducted at the end of each 5 min. session.

b

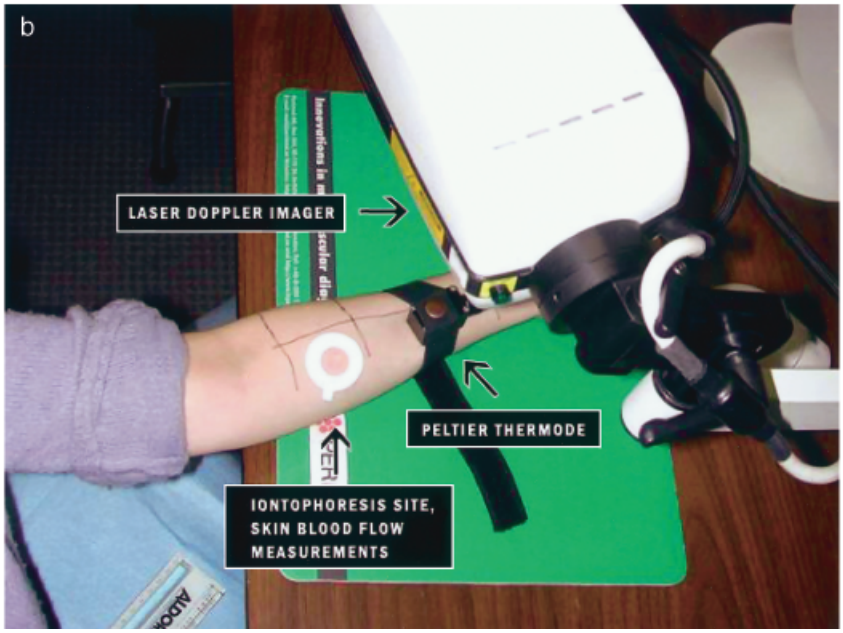


Figure 2
Skin areas of stimuli and measurement. (*a*) Experimental design. (*b*) Demonstrates the area of histamine iontophoresis and the site of the Pelteir thermode distal 3 cm away from the area of skin blood flow measurement.

Psychophysical assessment Psychophysical assessment of itch was performed with a COVAS (Medoc, Ramut Yishai, Israel). Subjects use the COVAS by sliding a mobile lever across a horizontal 10 cm line long their perception of the intensity of itch during the experimental stimulus. The scale indicates "no sensation" on the left and "strongest imaginable sensation" on the right.

Subjects first participated in a psychophysical training session in which they rated four stimuli applied to their non-dominant volar forearm: 2°C, 15°C, 41°C, and 49°C for 30 s each at 30 s intervals. A two-column grid of 5 cm boxes (total of six boxes) was then sketched onto each subjects' forearm (see Fig 2). Subjects were then asked to rate only their itch with and without the stimuli over a period of 5 min in which each different stimulus was "on" for 30 s followed by a 30 s "off" interval.

Experimental procedure (see Fig 2) Subjects' forearms rested on an examination table at a vertical distance of about 15 cm from the imager arm. A baseline evaluation was then obtained in an area 3 cm outside of those areas where thermal stimuli and scratching were conducted in the same site where histamine iontophoresis would be later administered. Thermal stimuli of 41°C, 15°C, 49°C, and 2°C were initially applied, in that order, to different grid spaces using the TSA II Neurosensory Analyzer (Model TSA-2001, Medoc). Measures of blood flow utilizing the LDPI were recorded after each stimuli.

Scratching was performed with the use of a 7-in cytology brush (24–2199) (General Medical Corporation, Los Angeles, California). Uniformity was ensured by using pressure sufficient enough to crumple the skin-facing brush bristles to the point where the brush handle touched the surface of the skin. Controlled scratching was administered in circular motions throughout the scratching interval. During this cycle skin blood flow was measured.

The next experiment was measuring skin blood flow and itch intensity ratings using the COVAS 5 min after histamine iontophoresis for baseline itch, followed by administering histamine with the four thermal stimuli and scratching. This sequence of stimuli application was randomized among subjects and was initiated 30 s after completion of iontophresis. These stimuli and measurements were done in different grid spaces and the skin blood flow and itch intensity were recorded immediately after the stimuli. All external stimuli were introduced 3 cm distal to the iontophoresis stimuli; blood flow measurements were performed at the site of the iontophoresis stimuli. Each itch trial was separated by 10 min.

Statistical analyses Statistical analyses were performed by a statistician with Windows statistical software (Microsoft Corporation, Redmond, Washington) using two sample *t* test, analysis of variance, and the Pearson correlation test. Data are presented as mean $\pm$ SD; $p < 0.05$ is considered statistically significant.

Special thanks to Chan Yiong Huak, PhD, and Vishal Khana for their invaluable help in the statistical analysis and figure preparations.

DOI: 10.1111/j.0022-202X.2005.23942.x

Manuscript received December 21, 2004; revised June 24, 2005; accepted for publication July 22, 2005

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